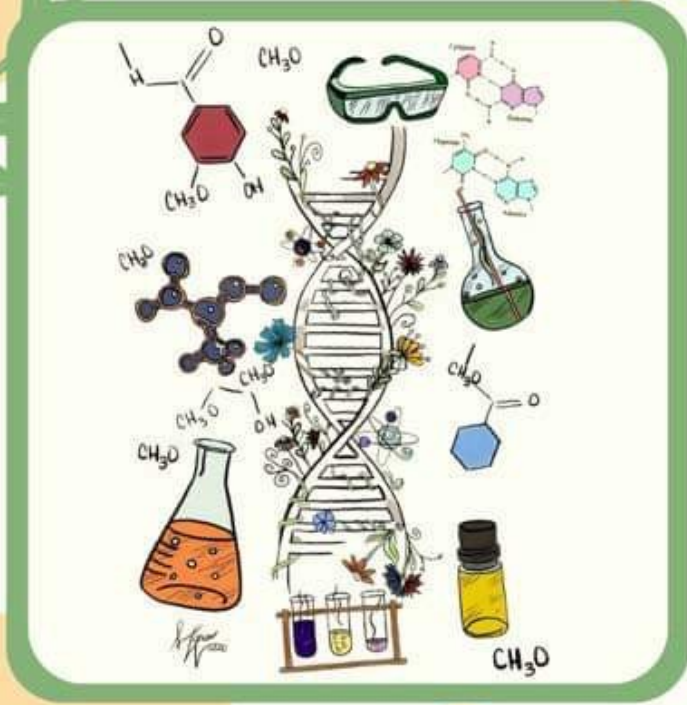


تفريغ عقاقير



Indole and proto
alkaloids

اسم الموضوع:

إعداد الصيدلاني / ة: ياسمين خليل



لجان الرفعات

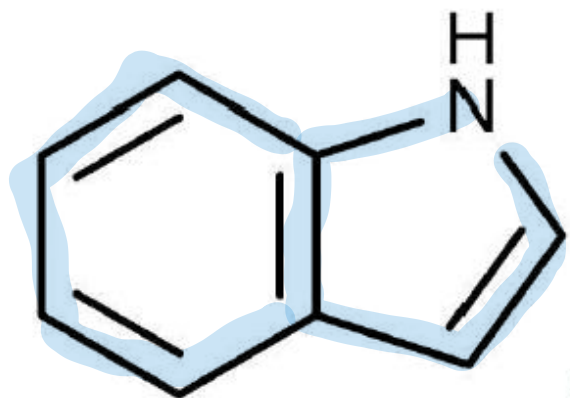
صلة بنزين + صلة فاسيفينها ل

Indole and proto alkaloids

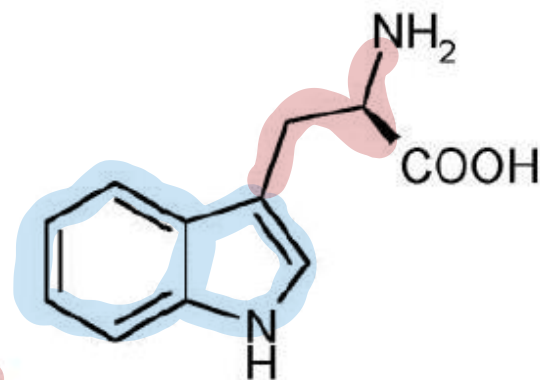
Tryptophan derived alkaloids

- Indole and Quinolines alkaloids are derived from the same amino acid which is **tryptophan**.
- Indole alkaloids are widely distributed among the **Apocynaceae**, **Loganiaceae** and **Rubiaceae** families.

سؤال امتحان؟
 Indole is derived from which amino acid? **Tryptophane**



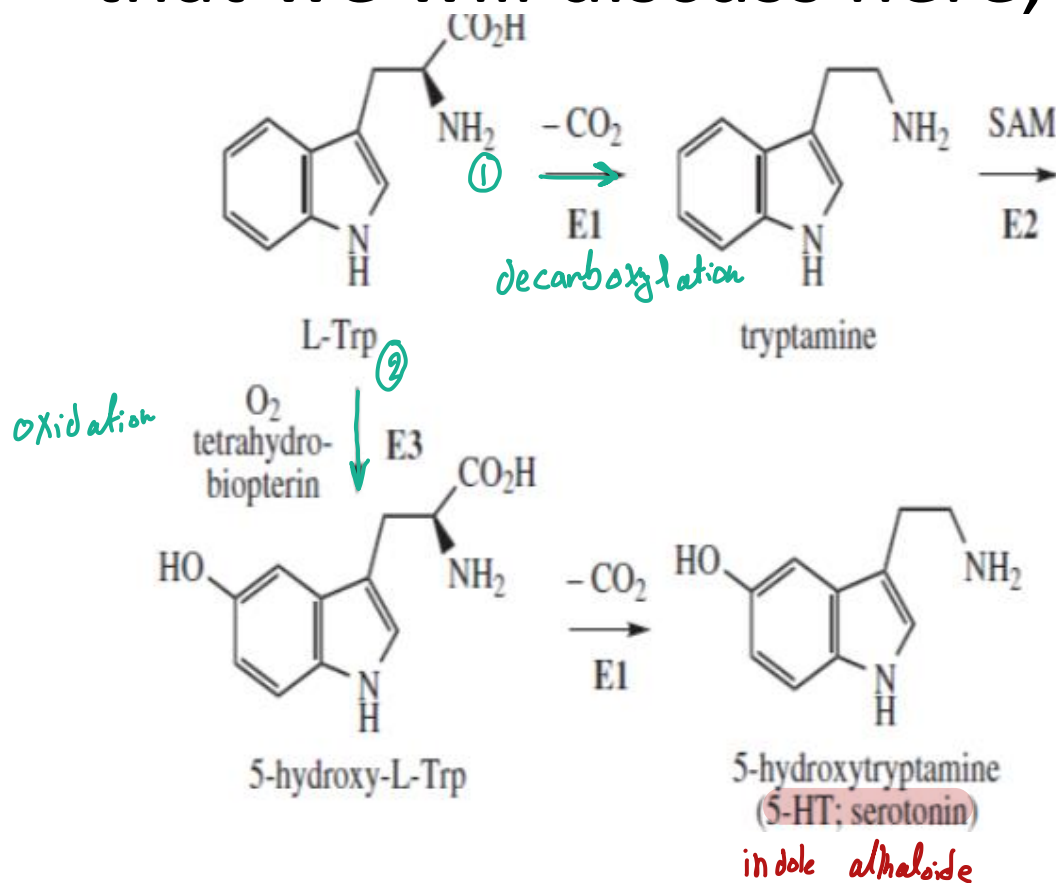
← **indole**



← **tryptophan**

طرق تصنيع indole هم طريقتين :-

- Tryptophan has 2 possible pathways to end up with the formation of our simple derivatives that we will discuss here,



① Tryptophan then decarboxylation to give tryptamine then hydroxylation to get 5-hydroxy tryptamine (5-HT, Serotonin)

②

Oxidation of tryptophan then decarboxylation to get serotonin (5-HT)

↓ نفس الكلام تحت

Synthesis of Serotonin

- first it can be decarboxylated to obtain tryptamine further reactions include oxidation will end up with 5-hydroxytryptamine (**serotonin** our first simple derivative)
- Or it can be first hydroxylated to 5-hydroxytryptophan → further decarboxylation will also lead to serotonin.

- Indole alkaloids derivatives including melatonin, serotonin & physostigmine
- These are simple derivatives of the amino acid tryptophan which are primarily obtained by
① decarboxylation of the amino acid tryptophan to obtain typtamine and then further modification especially oxidation at position ④ or at position ⑤.
②

5-Hydroxytryptamine

5-HT, Serotonin

Central NS موجود في
Peripheral NS
يعني بالتالي يحيط بالكلية
Central + peripheral

نقل عصب

- 5-HT, serotonin is a monoamine neurotransmitter found in cardiovascular tissue, the peripheral nervous system, blood cells, and the central nervous system.

- It mediates many central and peripheral physiological functions, including contraction of smooth muscle, vasoconstriction, food intake, sleep, pain perception, and memory.

- Although** 5-HT may be metabolized by monoamine oxidase, platelets and neurons possess a high affinity 5-HT reuptake mechanism.

reuptake يعيد
+ metabolized
for serotonin
فيقل تركيزه ولفظه

العادة ياتي مسبقا ما يكون طويلة

- This mechanism may be **inhibited**, thereby increasing levels of 5-HT in the central nervous system, by widely prescribed **antidepressant** drugs termed **selective serotonin re-uptake inhibitors (SSRIs)**.

- PROZAC®** which contains **Fluoxetine** which is a **selective serotonin re-uptake inhibitors (SSRIs)** officially approved for treatment of **depression**.

من الامثلة على هائي الادوية
Prozac
(fluoxetine)
صف

فالطباء اعمدوا لغيرها بأشياء يديم اصحاب العادة هاد
فصار عنا selective serotonin reuptake inhibitors
[SSRIs]
anti depressant
• أدوية

Serotonin derivatives

شقیقه - (صداع درده کوخ)

- **Migraine** headaches that do not respond to analgesics may be relieved by the use of an **agonist of the 5-HT₁ receptor**, since these receptors are known to mediate **vasoconstriction**.

analgesic
طایفه مع
و تبدیل

- **Sumatriptan** is used to treat migraine

- Sumatriptan is produced through methylation of 5-HT and turning the amino group into a tertiary one^①, and the hydroxyl group on carbon # 5 will be replaced by a sulphate group^②

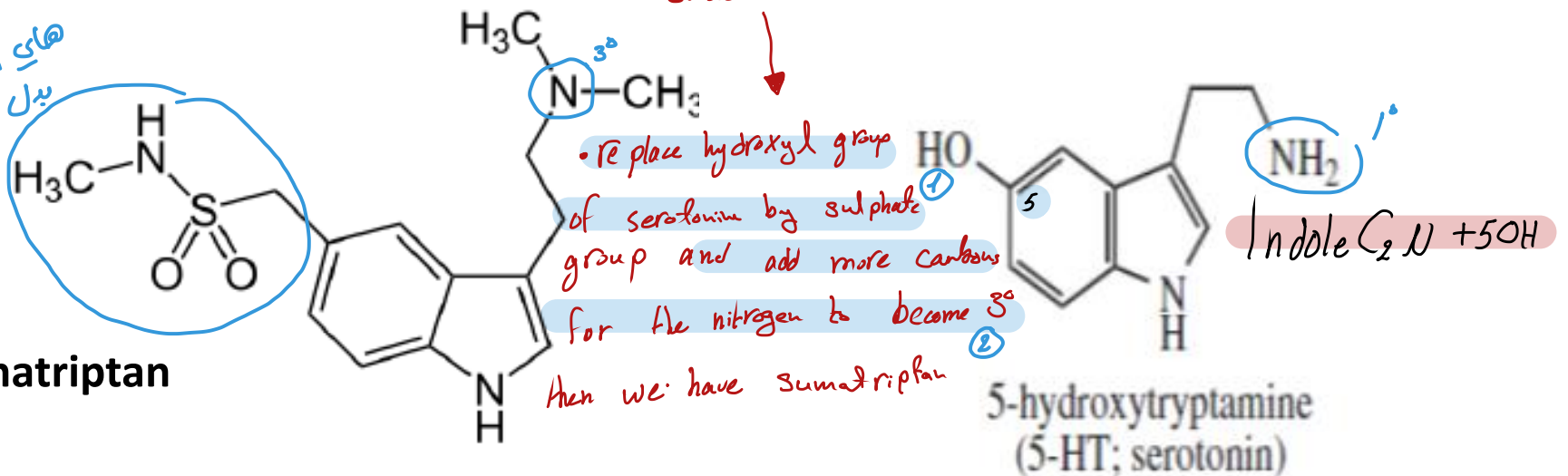
جایگزین
Sumatriptan

← ? serotonin is

- One of its benefits is that it is used for the treatment of acute migraine attacks

• The difference between these two structures is:

های اجته
بیل الهایدو کسل (OH)



Sumatriptan

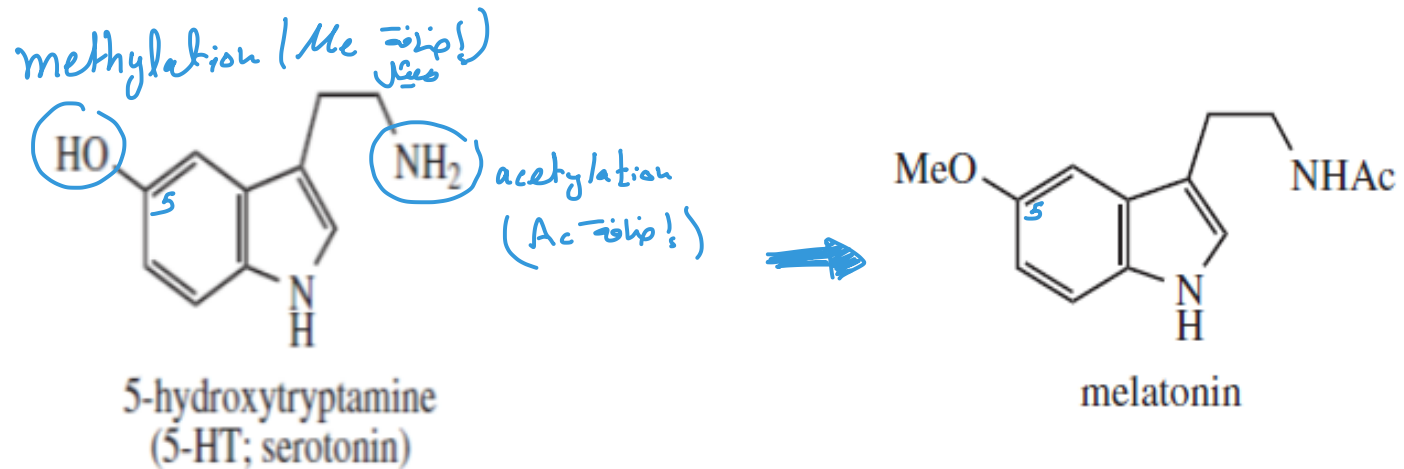
5-hydroxytryptamine
(5-HT; serotonin)

← نأخذها ونأخذها إلى عينها في كل النهر
sleeping pills

Melatonin

(the second simple derivative)

- In animals, **melatonin** is a hormone synthesized by the pineal gland in the brain.
regulation of body rhythm
غدة صنوبرية
- it can be synthesized by **methylation** of the 5-OH and **acetylation** of the amino group of the serotonin.
1
2



Melatonin

- Melatonin is claimed to be effective in helping to regulate disrupted circadian rhythms and **sleep disorders**. A slow-release formulation is available for treating insomnia in older patients; melatonin production is found to **decrease with age**.

أمره مع التجارب بالمرأة في كل ما تقدمنا بالهرمات ساعات النوم أقل

- It is currently also popular to reduce the effects of **jet-lag** by resetting the internal body clock.

الساعة البيولوجية للجسم
معللاً بين الزمان والحين في ساعات
إننا متضمن سفر بأفذه عشان ما نترن نوصته

Physostigmine (eserine)

- Isolated from the seeds of the *Physostigma venenosum*, this plant contains many alkaloids but the most important one is physostigmine.
- Physostigmine is a very unstable compound it oxidized easily,
- we can detect the deterioration of this compound by the color change that occurs due to oxidation therefore the oxidized derivative (rubreserine) can be easily recognized by its red color.

toxic

بغير لون أحمر

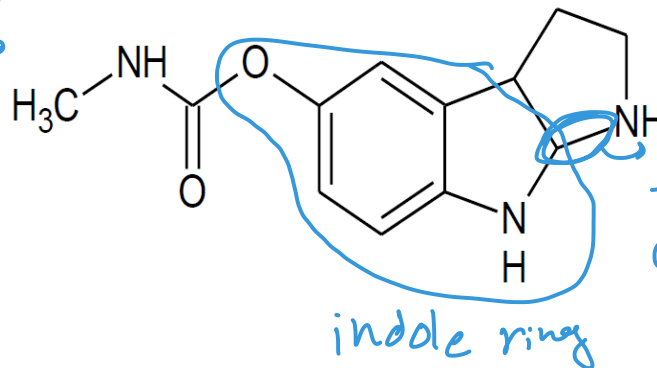
→ Oxidized form of physostigmine

① nucleophilic attack

في بترج، الدبل بوند من الاندول
وتتبعها بالنايتروجين

فبصيروا حلقة مغلقة

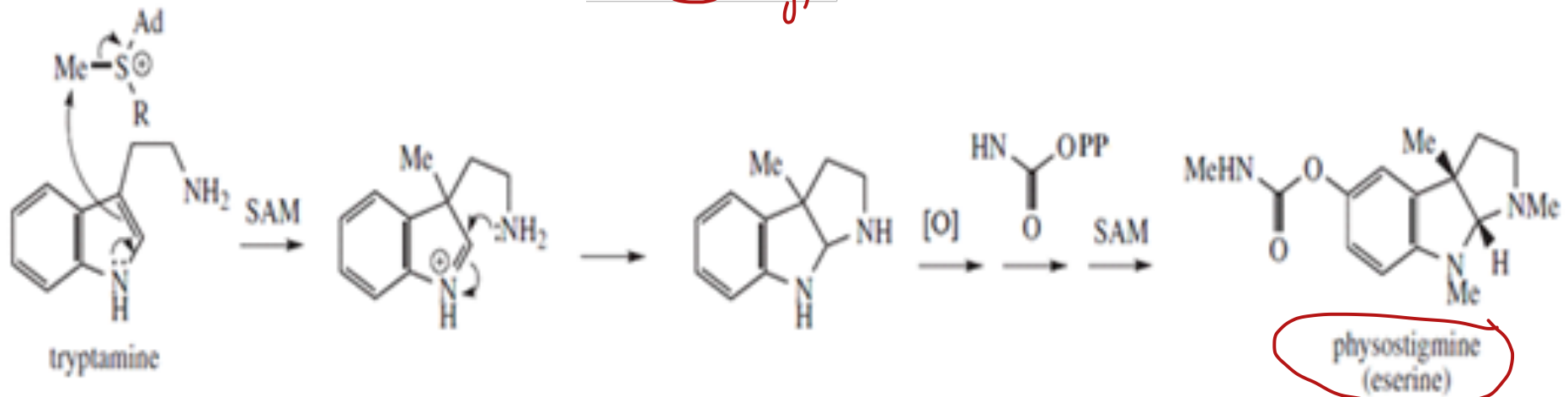
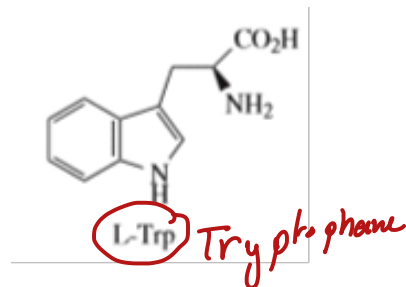
cyclization



دبل
بوند كانت
جدا الاندول

Physostigmine (eserine) :

- In the structure of the amino acid tryptophan (or its derivative tryptamine), ^{متجاور کربان} there are 2 adjacent carbons (the a & b carbons) of the NH group inside the indole ring, which are important nucleophilic centers because many of tryptophan



تثبيط انزيم
الاستيل كولين
بجس

↓ Physostigmine (eserine)

Acetylcholine esterase inhibitor

- Uses : physostigmine is the antidote for several anticholinergic compounds such as atropine hyoscyamine and related substances as well as it is an antidote for muscle relaxants like curare ①
- Moreover it is a transient (reversible) inhibitor of acetylcholinesterase, which mean that it will cause accumulation of Ach and this accumulation will enhance the memory & it is needed in the treatment of several disease like Alzheimer's disease ②
- This drug will not reverse the disease but it will delay it.

Not completely cure !!

toxic

Physostigma venenosum:

- From its name **venenosum**, it's **very toxic** plant, it comes from **seeds** of **calabar bean** (found in **Nigeria**), family: **Fabaceae**.

أحبنا سام لكشف الحقيقة

- This seeds are important as a source for **physostigmine**. It was used in **ordeal poison** by giving it to a person, if that person **vomiting** then he is **innocent**; if he **died** then he is guilty.

إذا أخذ الشخص هذه البذور واستقر في يعني هو بري؛ بس إذا صان يعني هو مذنب 🤔

- The person who eat this plant die due to **progressive paralysis** followed by **cardiac, respiratory failure**. Nowadays it's used as **rodenticide** (the **most** important use).

صبر قوارض

Common

Venca Alkaloids

from tryptophan ←

صناد سرطانين يمكن
يعمل سمية في الأخصاب

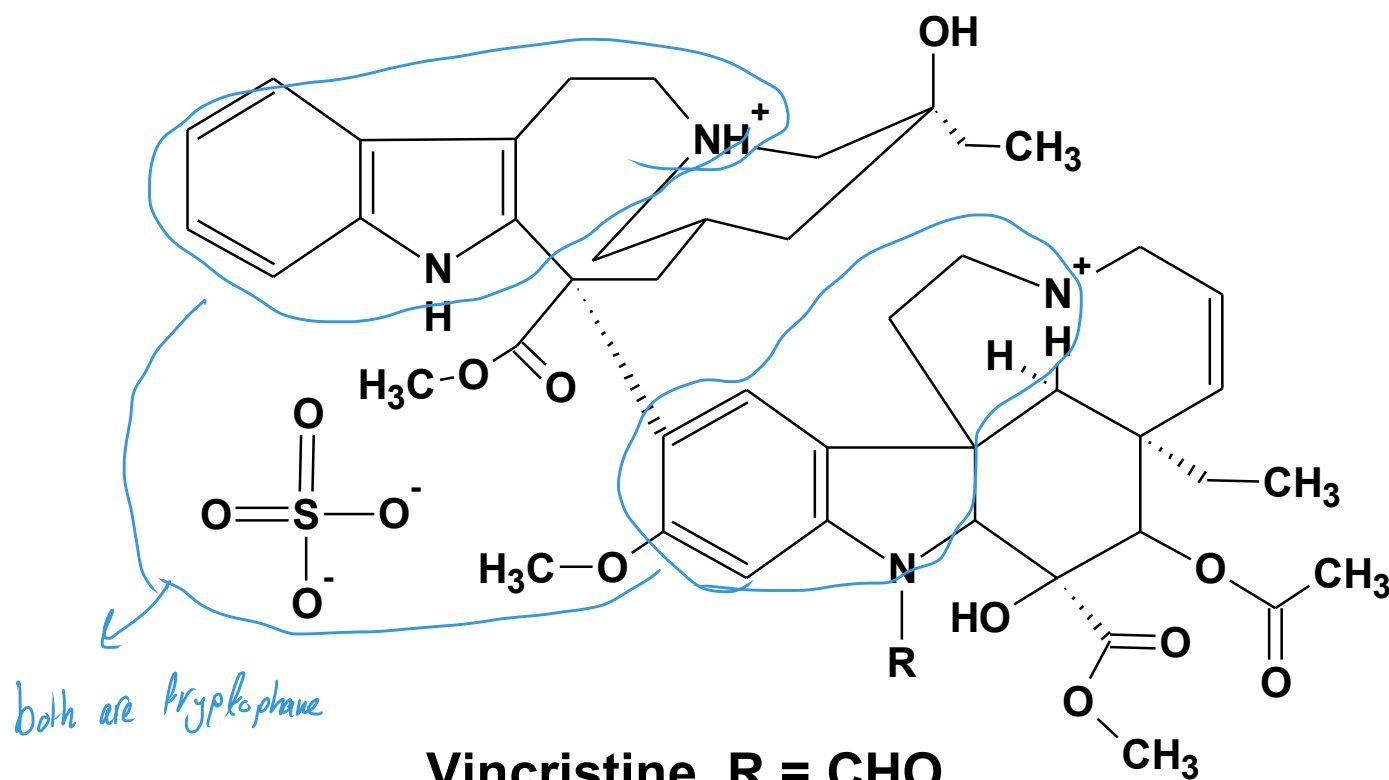
- **Vinblastine** and **Vincristine** are anti-cancer compounds from *Catharanthus raserus* and **Venca rosera**. they are antimitotic agents , but they cause serious neurotoxicity . ①
- other disadvantage ② of them is their low concentration in nature (we need 5000 Kg of their leaves to produce 1 g of them !!)
- Venicristine has more pharmacological activity than Viniblastine.

سؤال امتحان!

هناك structure لـ *Vinca rosea*؟



The alkaloids of the periwinkle plant (*Vinca rosea*)

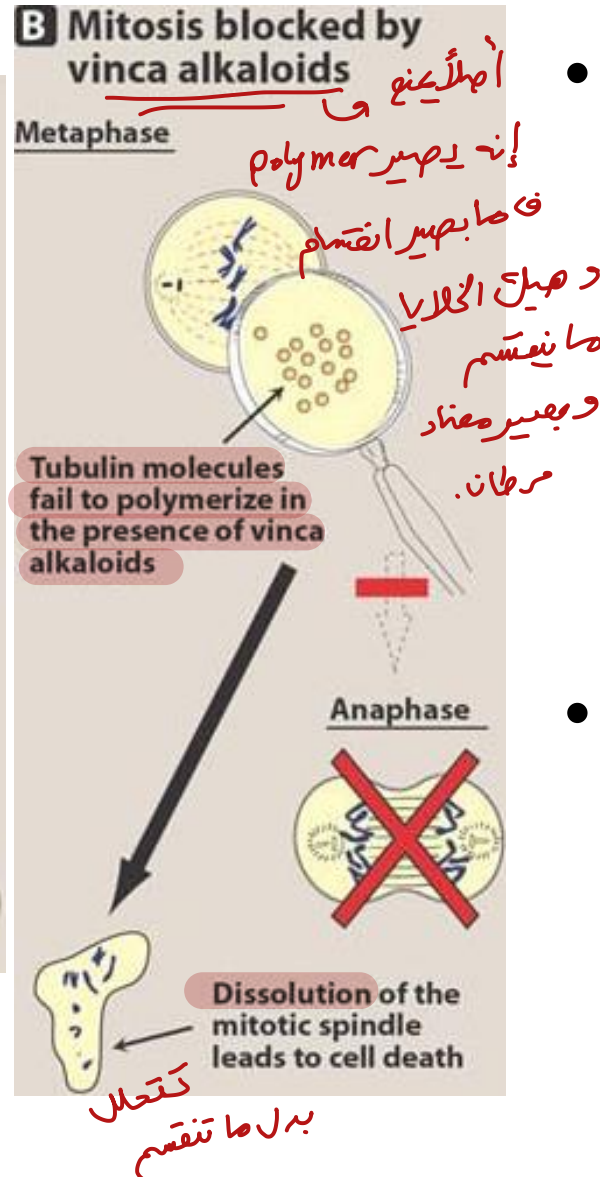
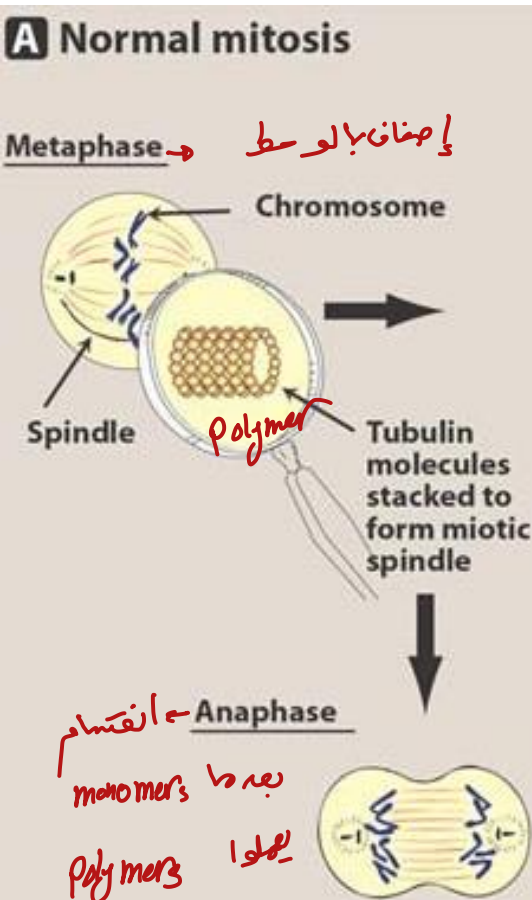


Vinblastine $R = \text{CH}_3$

They are dimeric indole-dihydroindole derivatives

يعني هنا جزئين indole جايين من tryptophane

Vinka alkaloids (Vinblastine, vincristine)



- These drugs block the formation of mitotic spindle by preventing the assembly of tubulin dimers into microtubules
- ***They act primarily on the M phase of cancer cell cycle



Meta phase

صحيح

Ergot alkaloids ergoline

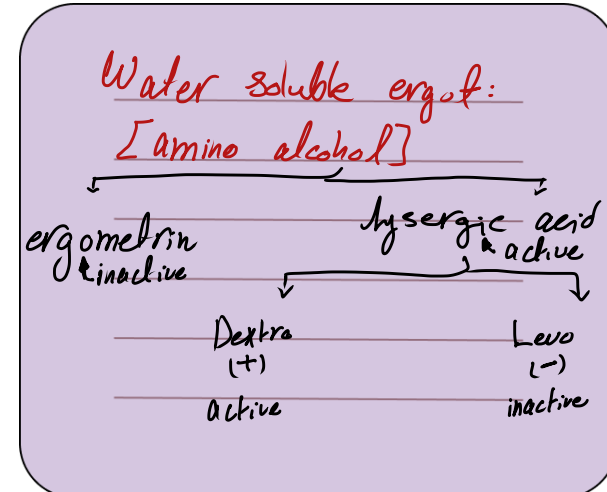
Claviceps purpurea fung

- Ergot alkaloids are isolated from infected plants (fungal infection). مسئله امتحان ٢٠٢٠ سؤال ١ ▼
- They are tryptophan derivatives

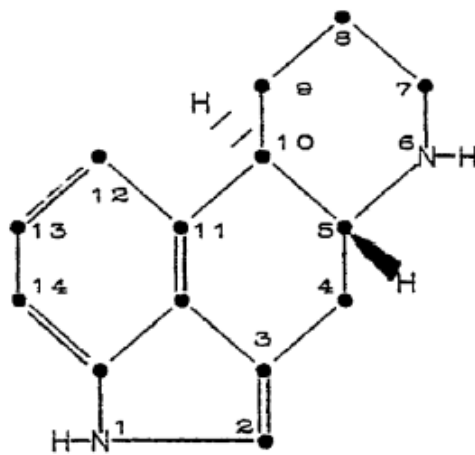
Ergot alkaloids

- Ergot alkaloids aren't naturally occurring; it's synthesis in response to infection by Claviceps purpurea fungus.
(fungal infection)
- **Ergot Alkaloids** in general are classified into **2** gp:
- 1. **water soluble gp** :due to presence of **amino alcohol** functional gp, it forms **20%** of total alkaloids, an example ^a**ergometrin**, **alcohol** alkaloids contain what is called ^b**lysergic acid**, this acid has **2** forms: **dextro(+)** which is the **active** form and **levo (-)** form is inactive

Lysergic acid

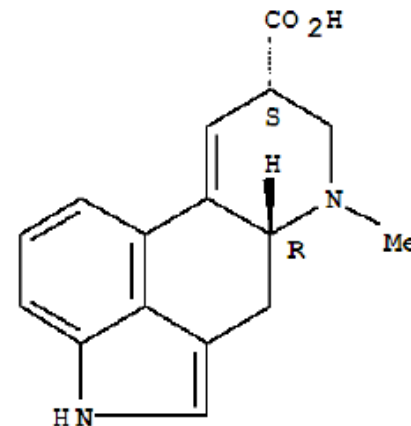


- Lysergic acid which is the **active** ingredient for **ergot** alkaloids may be exposed to some changes which is **enolization** (heat or alkaline effect), this will convert it to **inactive** compound called **isolysergic acid**.



active form
of ergot

enolization



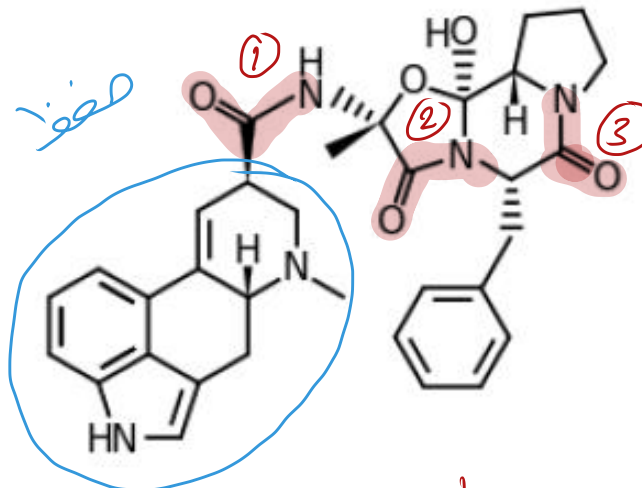
Isolysergic acid

inactive form

Ergotamine:

water in soluble

- 2. **Water insoluble gp**: It's a **peptide derivative** (contain an **amide group** and parts of **protein** and **amino acid**).
- Ergotamine:**
- It's a **peptide derivative** contain **tripeptide** fragments **bonded** to lysergic acid via **amid link**. It's used for migraine *تسكين*
- the **hydrolysis** of **peptide ergot** alkaloids will produce **lysergic acid** + **proline** + **phenylalanine** + **pyruvic acid** + **ammonia**

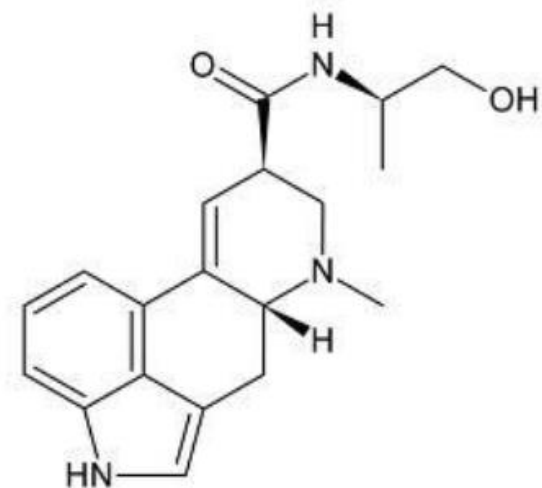


مركب ← *حمض الليسرجيك* + *تريبتيد* (3 amide groups) { *proline*, *phenylalanine*, *pyruvic acid + ammonia* }

Ergometrine

كانت النساء تستخدمه بعد الولادة معان
لمنع نزيف ما بعد الولادة [Vaso constriction]

- Ergometrine is used during the final stages of labour and immediately following childbirth, especially if haemorrhage occurs. Bleeding is reduced because of its vasoconstrictor effects, and it is valuable after Caesarian operations.

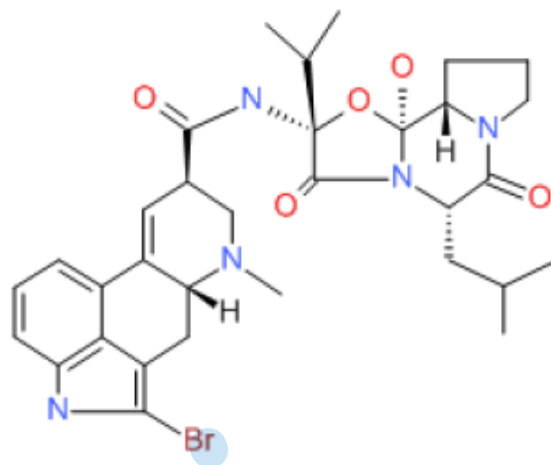


Ergometrine

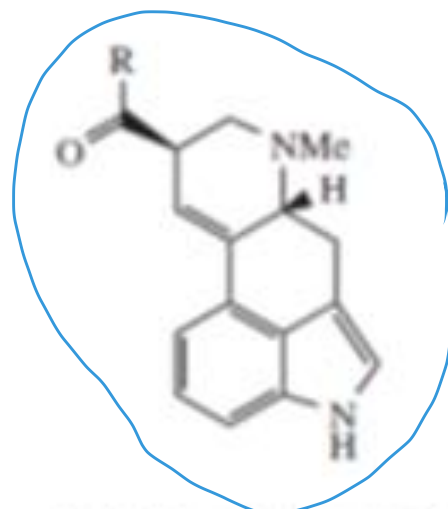
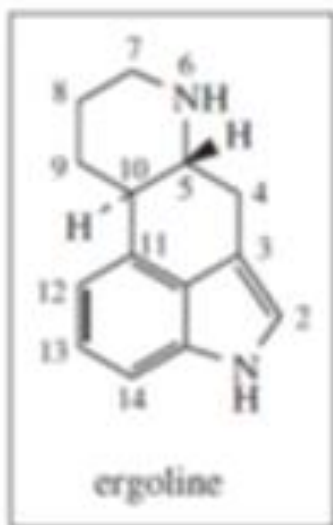
^{Br₂} Bromocriptine:

- It's very **cheap** compound, It's used to **inhibit prolactine** ^① production, also useful in treatment of **Parkinson disease** ^②
- It is a **dopamine agonist** ^③ that is used in the treatment of pituitary tumors, Parkinson's disease (PD), hyperprolactinaemia, and type 2 diabetes. ^③
- It has **bromine (Br)** at **C2**, **2 isopropyl** moiety at **peptide** compound..

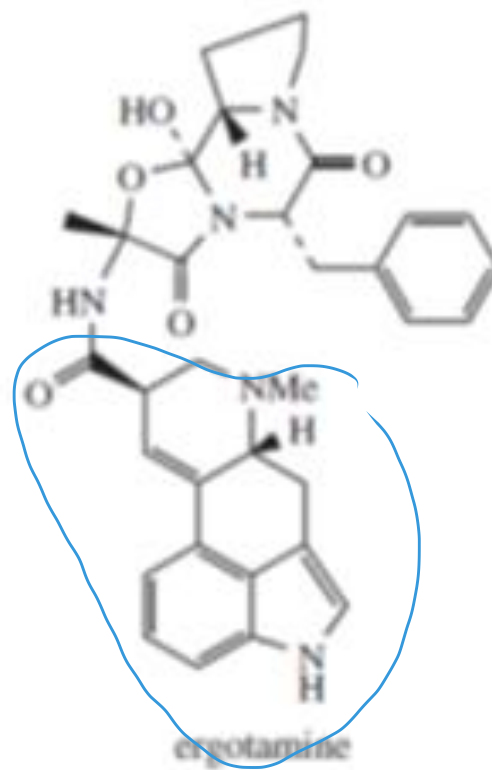
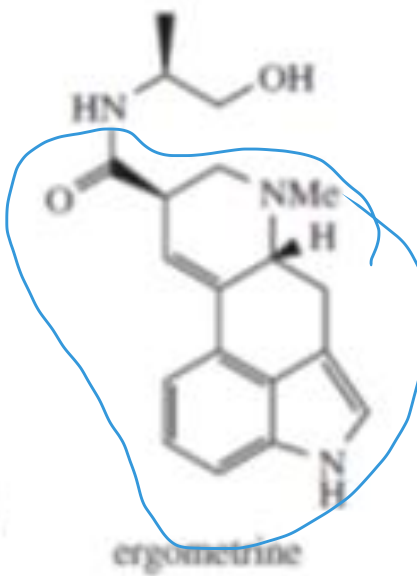
Bromocriptine is a semisynthetic derivative of a natural ergot alkaloid



Bromocriptine



R = OH, (+)-lysergic acid
R = NH₂, ergine



بدائية

يعني النيتروجين مش داخله بالحقه

بمن مصدرها

amino acid

[phenylalanine]

Proto alkaloids

- **proto** alkaloids (means the **nitrogen** is **not part** of heterocyclic structure) **derived from Phenylalanine**
- **Ehpedra: (family: Asteraceae)**
- It's very long plant, **leaves**, and **flowers** are considered as a **source for ephedrine**.
- Now it's known as **herbal ecstasy** because it has **CNS stimulant** and **hallucination**.

anti cough

نشوة

يعني بتخلي الدماغ

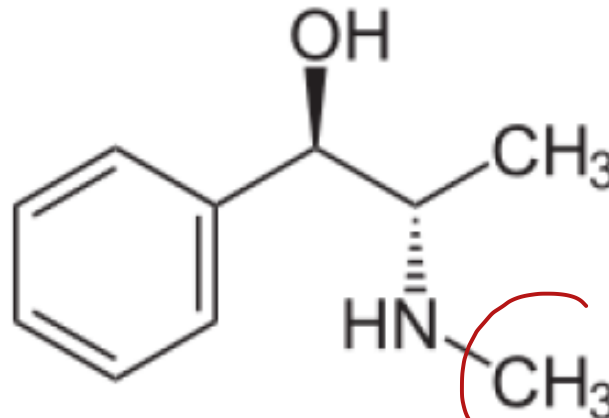
يصحح بمن بنفس

الوقت ملوحة.

Ephedrine (norephedrine)

مجموعه (methyl) - methyl

- Synthesis from **phenylalanine** that provide **C6C3** structure, or **C6C2** (by removing of carboxylate gp), or **C6C1**. So **phenylalanine** goes several steps, the first is removing of carboxylate gp then we add **amino gp** or alkyl gp to produce **norephidrine** then we add **methyl gp** to produce **ephedrine**.
صافها صافيل
فيها صافيل
- NOTE:** the active form of ephedrine is levo (-) form.



Ephedrine

drine:

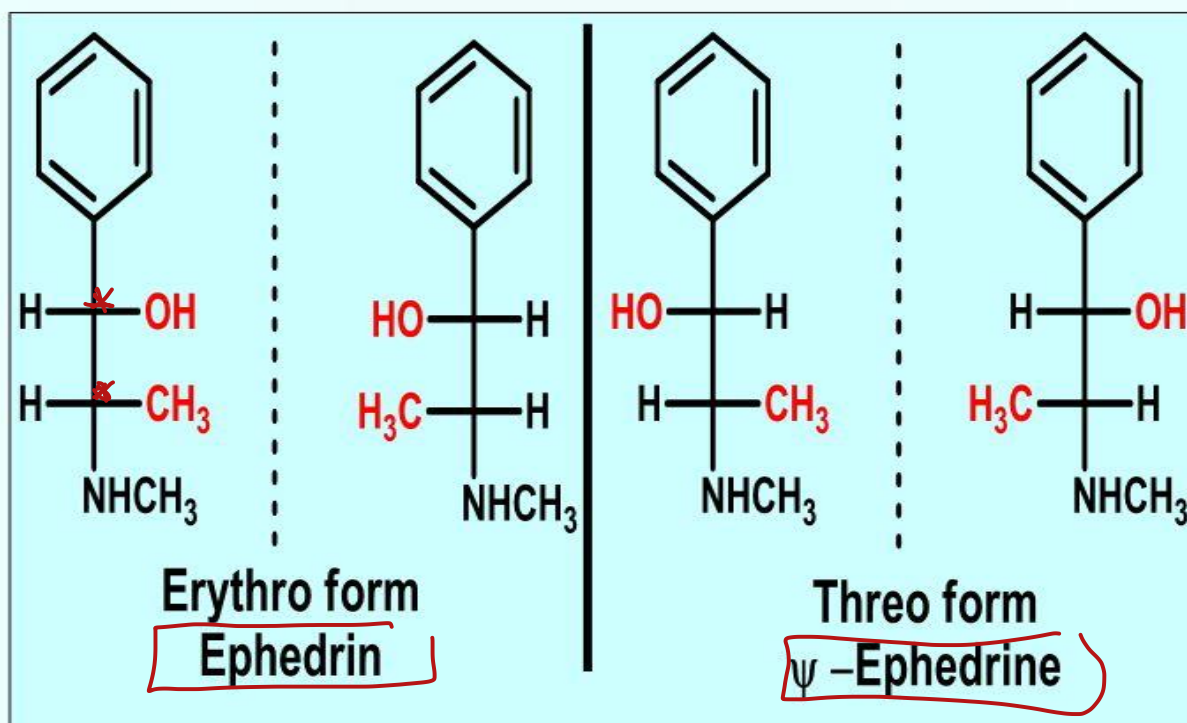
! ذل شافها

نور e phedrine
بدقه

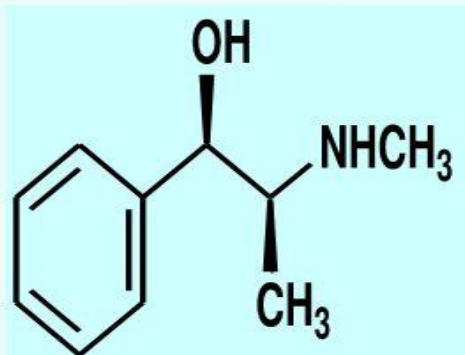
Ephedrine

Ephedrine has two (asymmetric) chiral carbons, so four stereoisomers (4 optically active isomers that exist as two pairs of enantiomers.)

- The erythro pair is known as ephedrine. *2 stereoisomers*
- The threo is known as pseudoephedrine (ψ -ephedrine). *and the other 2*



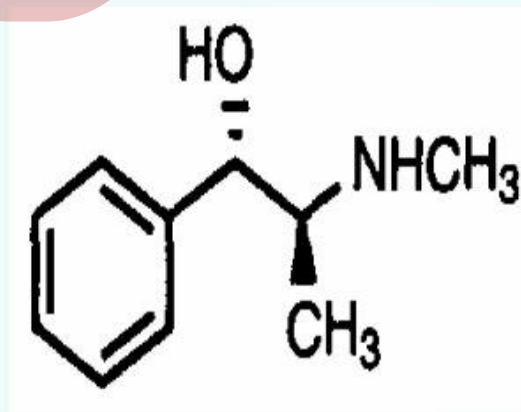
Ephedrine



- (-)-*Erythro*-2-(methylamino)-1-phenyl-1-propanol
- (-)-*Erythro*- α -[(1-methylamino)ethyl] benzyl alcohol.

- ☐ It is available as HCl or as Sulphate. Can U draw ???
- ☐ Used by injection and orally.
- ☐ Used as adrenergic, as vasopressor, cardiac stimulant, nasal decongestant and bronchodilator and CNS stimulant activity.
- ☐ in hypotensive conditions
- ☐ In allergic disorders, colds, nasal congestion
- ☐ In asthma
- ☐ in narcolepsy

Pseudoephedrine



(+)-*Threo*-2-(methylamino)-1-phenyl-1-propanol

(+)-*Threo*- α -[(1-methylamino) ethyl] benzyl alcohol

- Pseudoephedrine is the *threo*-diastereoisomer of ephedrine
- HCl and Sulphate salts
- has virtually no direct activity
- **Mainly indirect action.**
- widely used as nasal decongestant.

قات Catha edulis (celastraceae)

CNS stimulant

- A flowering plant contains alkaloid cathinone, a stimulant, which is said to cause excitement, loss of appetite, and euphoria

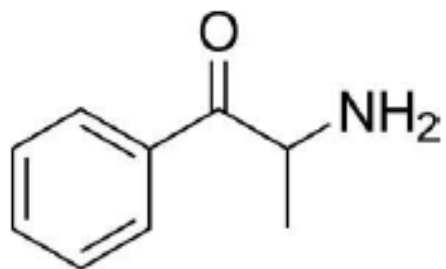
✓ L2

فئة سُخْفِي

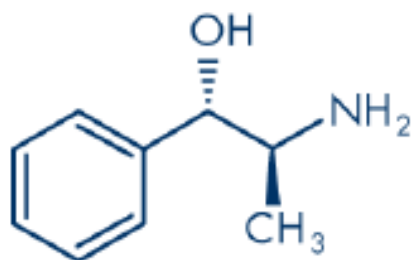


The main compounds in this plant are

Cathinone (ketonic) which is very similar to norepinephrine?



Cathine (alcoholic or reduced) form of pseudoephedrine.



- These two compounds have an effect on the brain barrier in the CNS, due to the similarity in structure with amphetamines (a compound already found on the nerve barriers); some people may take amphetamine supplements to have euphoria, restlessness and to stay awake for a long time. People can gain this effect by suckling the leaves of this plant.
- only fresh leaves contain cathinone and cathine, while the dried ones don't, and upon drying cathinone is converted to another derivative.

CNS
stimulated

بفضل بريد النخلة
يرجع يمس بالتخفيف الي
كان يحس ان صرة بين مع

• **Mechanism of action** : when cathonine attacks the barrier in the CNS, this attack will lead to high secretion of catecholamines ,with time, as a result tolerance might happen and the person need to take higher amount than the previous one. So who usually take cathonine for a long periods of time, will need higher doses due to tolerance. To stop the effect of Khat, take a CNS depressant; like barbiturates or opioids (compounds from opium like morphine) that terminate the effect of CNS depressant

- Khat is not used for its pharmacological effect anymore. In the past they used to use khat in the treatment of addiction, now it's abused because of the psychological dependence and some people may die because of the tolerance.

يا حيُّ يا قيُّومُ، بِرَحْمَتِكَ أَسْتَغِيثُ، أَصْلِحْ لِي
شَأْنِي كُلَّهُ، وَلَا تَكِلْنِي إِلَى نَفْسِي طَرْفَةَ عَيْنٍ

اللَّهُمَّ إِنِّي أَعُوذُ بِكَ مِنَ الْهَمِّ وَالْحَزَنِ، وَالْعَجْزِ وَالْكَسَلِ، وَالْبُخْلِ،
وَالْجُبْنِ، وَضَلَعِ الدَّيْنِ، وَغَلَبَةِ الرِّجَالِ.

اللَّهُمَّ أَنْتَ رَبِّي لَا إِلَهَ إِلَّا أَنْتَ خَلَقْتَنِي وَأَنَا عَبْدُكَ وَأَنَا عَلَى عَهْدِكَ وَوَعْدِكَ مَا اسْتَطَعْتُ
أَعُوذُ بِكَ مِنْ شَرِّ مَا صَنَعْتُ أَبُوءُ لَكَ بِنِعْمَتِكَ عَلَيَّ وَأَبُوءُ لَكَ بِذُنُوبِي فَاغْفِرْ لِي فَإِنَّهُ لَا
يَغْفِرُ الذُّنُوبَ إِلَّا أَنْتَ

سبحان الله

الحمد لله

لا إله إلا الله

الله أكبر

لا حول ولا قوة إلا بالله

اللهم اغفر لي ولوالدي وللمسلمين والمسلمات
والمؤمنين والمؤمنات الاحياء والاموات

والسلام عليكم ورحمة الله وبركاته